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EXAMINER

BEISNER, WILLIAM H

ART UNIT PAPER NUMBER

1744

DATE MAILED: 03/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/089,153

Applicant(s)

NORDON, ROBERT E

Examiner

William H. Beisner

Art Unit

1744

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 November 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 45-52 and 55-70 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 45-52 and 55-70 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 11/28/05.
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

1. The information disclosure statement filed 11/28/05 has been considered and made of record.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

3. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

Determining the scope and contents of the prior art.
Ascertaining the differences between the prior art and the claims at issue.
Resolving the level of ordinary skill in the pertinent art.
Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. Claims 45-52, 55-58 and 60-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Slowiaczek et al.(US 5,763,194) in view of Amiot et al.(US 5,202,254).

The reference of Slowiaczek et al. discloses a bioreactor for the proliferation of and growth of cells that includes the use of hollow fiber membranes for the containment of cells therein and formed of a semipermeable material that is permeable to at least nutrient, regulator or

Art Unit: 1744

metabolite and positioned within a housing to define an acellular space (See Figures 4 and 5 and column 11, lines 16-58). The housing has inlet and outlet structures communicating with the acellular space to define an acellular flow path (See Figures 4 and 5). The device includes a liquid flow circuit providing fluid communication with the inlet and outlet (See column 11, lines 23-26).

Claim 45 first differs by reciting that the semipermeable material is permeable to at least nutrient, regulator or metabolite but is not permeable to at least protein required for proliferation, differentiation and/or genetic modification.

The reference of Amiot et al. discloses that it is known in the art to culture cells on one side of a semipermeable membrane wherein media containing oxygen, nutrients and other chemical stimuli is transported through the semipermeable membrane from a media side to the cell side and while waste products and contaminating proteins are transported from the cell side to the media side of the membrane (See column 1, lines 16-46). The reference also discloses that the molecular weight cut-off of the membrane is chosen so as to provide the transfer discussed previously while maintaining cellular product and serum on the cell side of the membrane (See column 1, lines 34-39, and column 6, lines 49-56).

In view of this teaching, it would have been obvious to one of ordinary skill in the art to modify the molecular weight cut-off of the membrane of the primary reference for the known and expected result of providing a membrane that maintains cellular product and/or growth factor (serum) on the cell side of the membrane while still providing for the exchange of cell nutrients and waste products as is contemplated by the reference of Amiot et al.

Claim 45 further differs by reciting that the circulation system that circulates media through the acellular space is responsive to the oxygen uptake, metabolite uptake and/or lactate output of the cells being cultured.

The reference of Amiot et al. discloses that it is known in the art to determine the glucose utilization and lactate production rates in a hollow fiber bioreactor device and adjust the medium feed rate in response to these measured rates (See column 7, lines 7-19).

In view of this disclosure, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the system of the modified primary reference so that the circulation system for the acellular space is responsive to the cell biomass for the known and expected result of maintaining predetermined metabolite levels. Note whether the response is provided manually or by automated means is not sufficient to patentably distinguish over the prior art references because providing an automatic or mechanical means to replace a manual activity which accomplished the same result is not sufficient to distinguish over the prior art. In re Venner, 262 F.2d 91, 95, 120 USPQ 193, 194 (CCPA 1958).

With respect to claim 46, the combination of the references as discussed above would result in a device wherein the lumens of the hollow fibers contain cells and at least one protein required for proliferation, differentiation and/or genetic modification of the cells.

With respect to claim 47, the combination of the references as discussed above would result in a device wherein the acellular space would contain media including at least one substance required for the proliferation of the cells.

With respect to claim 48, the substance can be oxygen, glucose or amino acids (See column 11, lines 28-29, of Słowiacek et al.).

With respect to claims 49 and 50, the hollow fiber membrane can be cellulose (See column 2, lines 28-34, of Slowiaczek et al.).

With respect to claim 51, in the absence of a showing of criticality and/or unexpected results, it would have been obvious to one of ordinary skill in the art to determine the optimum dimensions of the hollow fiber membrane while providing the required molecular weight cut-off and maintaining the structural integrity of the fibers.

With respect to claim 52, the reference of Amiot et al. discloses that the use of pumps for circulating media relative to the acellular side of the membrane in a culture device is conventional in the art. As a result, it would have been obvious to one of ordinary skill in the art to employ a pump in the system of the modified primary reference for the known and expected result of providing an art recognized means for circulating the culture media within a membrane bioreactor system.

With respect to claims 55-58, the reference of Amiot et al. discloses the use of a gas exchange cartridge (38, 56) for controlling the oxygen and carbon dioxide content of the acellular media. The use of silicone membranes in oxygenation devices is notoriously well known in the art and would have been obvious for the known and expected result of providing an art recognized structure for oxygenating the culture media.

With respect to claim 60, the acellular media is recycled (See Figures 1, 2 and 3 of Amiot et al.).

With respect to claim 61, the reference of Amiot et al. discloses that the use of a pump and inlet (66) is known in the art for adding fresh media. As a result, it would have been obvious to provide the system of the modified primary reference with a means for adding fresh medium

Art Unit: 1744

for the known and expected result of replacing spent media over the length of the culture process.

With respect to claims 62-65, the lumens of the hollow fibers include ligands (See column 2, lines 41-45; Figure 5; and column 11, lines 16-59, of Slowiaczek et al.).

With respect to claims 66-68, the cells are haematopoietic cells (See column 11, lines 46-59, of Slowiaczek et al.).

With respect to claim 69, the device is capable of both cell separation and culture.

With respect to claim 70, in the absence of further positively recited structure, the device is considered to be portable.

5. Claim 59 is rejected under 35 U.S.C. 103(a) as being unpatentable over Slowiaczek et al.(US 5,763,194) in view of Amiot et al.(US 5,202,254) taken further in view of Gebhard et al.(US 5,126,238).

The combination of the references of Slowiaczek et al. and Amiot et al. has been discussed above.

Claim 59 differs by reciting that the device includes a device for controlling the temperature of the culture media.

The reference of Gebhard et al. discloses that it is conventional in the art to employ a loop heater for controlling the temperature of the culture media (See column 8, lines 19-27).

In view of this teaching, it would have been obvious to one of ordinary skill in the art to provide the system of the modified primary reference with a heater device for controlling the

Art Unit: 1744

temperature of the culture media for the known and expected result of maintaining the viability of the cells by maintaining proper culture conditions including temperature.

Response to Arguments

6. With respect to the rejection of claims 45-70 under 35 USC 112, second paragraph, Applicants' amendments and associated comments (See pages 7-8 of the response filed 11/28/05) are sufficient to overcome the rejection of record.

7. With respect to the rejection of claims 45-53, 55-58 and 60-70 under 35 USC 103 over the combination of the references of Slowiaczek et al. and Amiot et al., Applicants argue (See pages 8-11 of the response filed 11/28/05) that the rejection is improper for the following reasons:

- a. The reference of Slowiaczek et al. is focused on cell separation rather than on cell culture while the instant invention is focused on cell culture.
- b. While the reference of Slowiaczek et al. states that cells may divide and multiply, the reference does not suggest that cells may be grown to concentrations considerably greater than conventional culture systems by the provision of a semi-permeable material being permeable to nutrient, regulator or metabolite but not permeable to protein required for proliferation.
- c. The reference of Slowiaczek et al. fails to suggest that the perfusion rate is controlled as claimed in instant claim 45.

Art Unit: 1744

- d. The reference of Amiot fails to cure the deficiencies of the reference of Slowiaczek et al. because the cells of Amiot are inoculated into the extracapillary space and the method of Amiot requires two media circulation loops.
- e. Neither of the references of Slowiaczek et al. or Amiot suggests the advantages of the instant invention. Applicants stress that neither references suggests intracapillary growth of cells, especially, since Amiot discloses extracapillary growth.
- f. The combination of the references of Slowiaczek et al. and Amiot fail to teach or suggest a) intracapillary growth of cells; b) a single flow path of media through the extracapillary space; c) circulation that is responsive to cellular biomass; and d) integration of cell separation and expansion as a single platform.

In response to argument a) above, while the device of the reference of Slowiaczek et al. is used for cell separation, the reference also discloses cell culture or expansion after separation of the cells (See column 11, lines 16-59). Note Applicants' own invention also involves cell separation in addition to culture.

In response to argument b) above, as argued immediately above, the reference of Slowiaczek et al. discloses multiplication of the cells within the device. The reference of Amiot suggests the use of a membrane for retaining the cell growth proteins within the cell culture space. Note one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Furthermore, Applicants' allegations of unexpected results have not been supported by factual evidence.

Art Unit: 1744

In response to argument c) above, the reference of Amiot was relied upon to suggest this claimed feature. Note one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to argument d) above, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The combined teachings of the reference of Slowiaczek et al. and Amiot meet the instant claim language.

In response to argument e) above, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

In response to argument f) above, the reference of Slowiaczek et al. discloses intracapillary growth of cells, a single flow path of nutrient medium through the extracapillary space of the device (See column 11, lines 16-59), and integration of cell separation and expansion as a single platform (See column 11, lines 16-59). The reference of Amiot discloses circulation that is responsive to cellular biomass (See column 7, lines 7-19).

Art Unit: 1744

8. With respect to the rejection of claim 54 under 35 USC 103 over the combination of the references of Slowiaczek et al., Amiot and Folena-Wasserman et al., this rejection has been withdrawn since the claim has been cancelled.

9. With respect to the rejection of claim 59 under 35 USC 103 over the combination of the references of Slowiaczek et al., Amiot and Gebhard et al., Applicants argue (See page 12 of the response filed 11/28/05) that the reference of Gebhard et al. does not cure the deficiencies of the combination of the references of Slowiaczek et al. and Amiot.

In response, for reasons already of record, the Examiner is of the position that the combination of the references of Slowiaczek et al. and Amiot meet the limitations of claim 45. The reference of Gebhard et al. was cited to address the limitations of dependent claim 59.

Conclusion

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,


Art Unit: 1744

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to William H. Beisner whose telephone number is 571-272-1269. The examiner can normally be reached on Tues. to Fri. and alt. Mon. from 6:15am to 3:45pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Richard Crispino can be reached on 571-272-1226. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


William H. Beisner
Primary Examiner
Art Unit 1744

WHB